App. No. 10/530,785

REMARKS

Favorable reconsideration is respectfully requested in view of the above amendments and following remarks. Claims 1-22 have been canceled without prejudice or disclaimer. Claims 23, 25 and 26 have been amended editorially. No new matter has been added. Claims 23-26 are pending.

Claims 23-26 are rejected under 35 U.S.C. 103(a) as being obvious over Hashimoto et al. (WO 02/44167). Applicants respectfully traverse the rejection.

Claim 23 is directed to a process for producing an amorphous optically active isomer of lansoprazole. Claim 23 requires the amorphous optically active isomer of lansoprazole to be obtained from hydrated crystals of optically active isomer (R-isomer) of lansoprazole.

The advantages of the method are explained as follows. In conventional methods, although lansoprazole R-isomer can be synthesized as an amorphous form at first, it becomes difficult to synthesize as an amorphous form after producing the crystals of anhydrous lansoprazole R-isomer (see page 44, lines 3-6 of the present specification; see also WO 00/78745). This is a general phenomenon, and once crystals have been given, it is usually difficult to synthesize an amorphous substance with the same method (see page 44, lines 6-9 of the present specification). That is, anhydrous lansoprazole R-isomer will not convert to an amorphous form by heating directly, and when a solution containing lansoprazole is concentrated, an amorphous substance cannot be synthesized by a conventional method once they have been crystallized (see page 44, lines 9-15 of the present specification).

However, Applicants have unexpectedly found that an amorphous lansoprazole can be produced from hydrated crystals of optically active isomer (R-isomer) of lansoprazole (see line 16 of page 44 to line 9 of page 45 of the present specification). Advantageously, the method allows for plant scale production of the amorphous optically active isomer of lansoprazole without difficulty.

Hashimoto is directed to obtaining stable crystals, as opposed to the amorphous form, of optically active isomer of lansoprazole by crystallizing out of a given organic solvent solution containing optically active isomer of lansoprazole in a given concentration at a given temperature. In particular, Hashimoto describes in detail the preparation of (R)-lansoprazole

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or (S)-lansoprazole that can be used as a starting material in their crystal production method from line 19, page 5 to line 13, page 17 of the reference.

While the reference notes that the (R)-lansoprazole or (S)-lansoprazole produced as the starting material may be a solid (crystal, amorphous) or an oily substance (see page 8, lines 15-23 of Hashimoto) and that in further preparation of the starting material, the thus-obtained crystal may be used as it is, dried or recrystallized where necessary (see page 14, lines 1-5 of Hashimoto), there is no experimental work or detailed explanation suggesting that an amorphous optically active isomer of lansoprazole can be obtained from hydrated crystals of optically active isomer (R-isomer) of lansoprazole. As noted above, it has been well established that once crystals have been given, it is usually difficult to synthesize an amorphous substance directly. On the other hand, Applicants have unexpectedly found that an amorphous lansoprazole can be produced from hydrated crystals of optically active isomer (R-isomer) of lansoprazole. Accordingly, claim 23 and the dependent claims therefrom are patentable over Hashimoto.

Claims 23-26 are rejected under 35 U.S.C. 103(a) as being obvious over Fujishima et al. (WO 00/78745). Applicants respectfully traverse the rejection.

Fujishima is likewise directed to producing the crystals, as opposed to an amorphous form, of anhydrous lansoprazole R-isomer as described in Examples 1 and 2 (see pages 15-17 of Fujishima). Fujishima teaches that the crystals of anhydrous lansoprazole R-isomer are obtained by using the starting materials described in Reference Examples 1 and 2, respectively (see pages 13-15 of Fujishima).

Reference Examples 1 and 2 describe preparation of an amorphous substance as a starting material for Examples 1 and 2. In particular, Fujishima describes dissolving racemic lansoprazole, fractionating the dissolved racemic lansoprazole by HPLC, followed by concentrating the obtained fractions to dryness so as to yield an amorphous substance. However, nothing in the reference teaches or suggests that an amorphous optically active isomer of lansoprazole can be obtained from hydrated crystals of optically active isomer (R-isomer) of lansoprazole.

In addition, at the time of filing of the present application, the conventional understanding in the art was that Fujishima's procedure of concentrating the obtained fractions to dryness does not allow for plant scale productions of the amorphous substance.

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For example, as described by Lee and Robinson in Oxford Chemistry Primer, Process and Development under Section 2.1.4, concentrating to dryness is difficult to achieve on a plant scale (for the Examiner's convenience, a copy of the relevant portions of the Lee and Robinson reference is filed herewith). On the other hand, the method of claim 23 uses hydrated crystals of optically active isomer (R-isomer) of lansoprazole as a starting material to produce the amorphous optically active isomer of lansoprazole, and does not require the procedures described by Fujishima. As such, the method of claim 23 advantageously allows plant scale productions of the amorphous optically active isomer of lansoprazole directly from hydrated crystals of optically active isomer (R-isomer) of lansoprazole without the difficulties in Fujishima's methods.

As discussed above, Fujishima fails to provide any teachings that would lead one to obtain an amorphous optically active isomer of lansoprazole from hydrated crystals of optically active isomer (R-isomer) of lansoprazole, much less any reason to expect that plant scale productions of the amorphous substance would be possible without concentrating the obtained fractions to dryness. Accordingly, claim 23 and the dependent claims therefrom are patentable over Fujishima.

In view of the above, favorable reconsideration in the form of a notice of allowance is requested. Any questions or concerns regarding this communication can be directed to the attorney-of-record, Douglas P. Mueller, Reg. No. 30,300, at (612) 455.3804.

52835
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Respectfully submitted,

HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. Box 2902
Minneapolis, MN 55402-0902
(612) 455-3800

Dated: Sept. 16, 2008

By: _____
Douglas P. Mueller
Reg. No. 30,300

DPM/ym

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Stan Lee and Graham Robinson are Senior Team Managers in the Process Development Department of Zeneca Pharmaceuticals.

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Process development: Fine chemicals from grams to kilograms

Stan Lee
Zeneca Pharmaceuticals, Macclesfield

Graham Robinson
Zeneca Pharmaceuticals, Macclesfield

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Series Editor's Foreword

There is no doubt that mankind has benefited tremendously from the contributions of synthetic organic chemistry to the quality of life. The discovery and synthesis phase is only the first step to producing a new pharmaceutical, equally important and demanding is the role of the process and development chemists whose efforts are crucial to bringing the new products to practical and commercial realization.

Oxford Chemistry Primers have been designed to provide concise introductions relevant to all students of chemistry and contain only the essential material that would normally be covered in an 8–10 lecture course. In this Primer, Stan Lee and Graham Robinson provide an excellent and entertaining account, through a number of case histories, of this enormously important area.

Dr Ray Bowle of Zeneca has been involved with many of the projects described in this primer. It is appropriate also to acknowledge his role in the whole Primer concept: without his affinity to convey his own enthusiasm for the Series to ICI plc and latterly to Zeneca the Series would never have been initiated or sustained. All the appreciative and master chemists who enjoy and benefit from the Primers owe him a debt of gratitude as I do.

Stephen G. Davies
The Dyson Perrins Laboratory, University of Oxford
October 1994

Preface

This book is largely derived from the study of compounds undergoing development as novel pharmaceutical agents within the Process Development laboratories of the Pharmaceuticals Division of ICI (Imperial Chemical Industries) and latterly within Zeneca Pharmaceuticals. It has been the privilege of the authors to report the results of many organic chemists within the Process Development Department. This book would not have been possible without their skills, dedication, ingenuity, and enthusiasm. We would also like to acknowledge the many helpful suggestions received from colleagues in both the contents and details of the book.

Our thanks are due to Dr Steve Davies for the opportunity to produce a contribution to the Primer series and for many helpful suggestions. Our thanks are also due to Dr Ray Bowle of Zeneca Pharmaceuticals for persuading us that the book would be a worthwhile task and fill a gap in the scant literature about Process Development.

S. A. L. and G. R. R.
Macclesfield
June 1994

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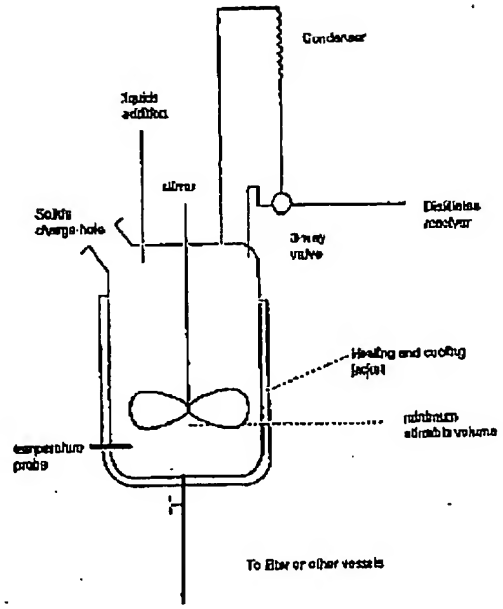

2.1.1 Separations

Metal vessels have the major disadvantage of being opaque and even a simple separation of an aqueous phase from an organic solvent is more difficult because the interphase cannot be seen in the vessel.

Separations are achieved by use of a clear sight-glass in the pipework leading from the bottom of the vessel. In extreme cases aqueous separations can be monitored by use of a conductivity probe to detect the solvent/aqueous boundary, which can then operate the appropriate valves to direct the aqueous phase to one vessel and the organic phase to a different vessel.

Water has a high electrical conductivity and most organic solvents have a very low conductivity. The probe can thus sense the change in conductivity at the interphase.

2.1.2 Volume measurement

This again is difficult because of the opaque metal. Some plant vessels have load cells fitted into the vessel supports which give an approximate measure of the *weight* of the vessel and its contents and thence a measure of changes in weight as solvent and reagents are added to or discharged from the vessel.

The load cell measures changes in the pressure (force) exerted by the vessel on its mountings. Changes in temperature can cause expansion of the metal which affects the accuracy of the readings.

A more primitive method is to use a calibrated dipstick. This is discouraged since it involves opening the reactor vessel and the stick becomes contaminated with the contents which may be hazardous.

Some special vessels are equipped with an ultrasonic system to measure liquid levels. Other techniques which have been applied for level measurement include use of methods based on radar or the use of a minute radioactive source.

2.1.3 Sampling

Opening of vessels to take samples is discouraged from an operational viewpoint because of the potential toxicity and flammability hazards of large-scale reactions. However, often it is essential to ensure that the reaction is proceeding normally, particularly during the first batches of a new process.

Some special vessels do have a fixed pipework system to enable samples to be taken or pH to be measured without opening the reactor, but these can be prone to erroneous results due to hold-up of liquids or solids in the pipes. The sample taken is thus not representative of the whole contents.

General purpose vessels can be sampled by use of a dip-can which is a small cylinder open at one end and attached to a long rod. This is lowered into the reactor and collects a sample of the reaction.

It is essential that the hazards of opening the vessel are considered and that the sampler wears suitable protective clothing.

2.1.4 Evaporation to dryness

This is a standard laboratory operation using a rotary evaporator. It is almost impossible to achieve on a plant scale. The vessel has to be fixed into the floor since it weighs several tons. Rotation of the vessel is thus impossible! The reactor vessel contains a stirrer, but this can only stir effectively when the liquid content is at least 10% of the total vessel volume. Thus removal of solvent by distillation will leave substantial quantities of solvent behind and evaporation to dryness is not possible. Additionally the best vacuum readily achievable is ca 30 mm Hg because of limitation of the capacity of pumps. Large vessels together with the associated pipework have many joints and these can give rise to minor leaks.

The effect of the residual solvent in the next stage of the synthesis is required evaluation.

A high boiling inert solvent (e.g. toluene) can sometimes be used to chase out a lower boiling reactive solvent.

2.2 Temperature

General purpose vessels usually have an operating temperature range of about +20°C to about 140°C and it is common that a synthetic process will be designed to operate within this temperature range. Higher temperatures are rarely necessary, but can be provided by the use of an electrically heated inert heating fluid (e.g. silicone based) circulating through the vessel jacket. Temperatures lower than +20°C are often required. Circulating chilled glycol through the vessel jacket is suitable for temperatures down to −15°C. Below this temperature special equipment is needed. Both glass and metal can become embrittled at low temperatures, and glass-lined metal vessels are very prone to cracking due to the different expansion coefficients. The usual method for very low temperature operation is to use a totally metal vessel

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